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Article

Evaluating the Correlation between PD-L1 Antibody Radiotracers and PD-1/PD-L1 Expression in Non-Small-Cell Lung Cancer: A Meta-Analysis

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Abstract: Non-small-cell lung cancer (NSCLC) accounts for the majority of lung cancer cases, with PD-1/PD-L1 immune checkpoint inhibitors playing a crucial role in treatment. Accurate assessment of PD-L1 expression is essential for patient stratification, yet traditional biopsies are limited by tumor heterogeneity. This meta-analysis evaluates the correlation between PD-L1 antibody radiotracers and PD-1/PD-L1 expression in NSCLC patients using PET/CT and SPECT/CT imaging. Analysis of four clinical trials involving 50 patients and six NSCLC samples revealed that higher SUVmax and T:BP ratios correlated with PD-L1 expression and prognosis, offering a more comprehensive and non-invasive alternative to biopsies. While promising, standardization of imaging parameters and further validation in diverse patient populations are needed to refine clinical application.

Keywords: PD-L1; PD-1; non-small-cell lung cancer (NSCLC); antibody radiotracers; PET/CT; SPECT/CT; tumor heterogeneity; SUVmax; T:BP ratio; immune checkpoint inhibitors; precision oncology

1. Introduction

Non-small-cell lung cancer (NSCLC) has represented roughly 85% of cases in all lung cancers [1]. In addition, NSCLC is not as sensitive to chemotherapy and radiation therapy as SCLC, and still has drastically low rate of patients who has complete response (CR) after treatments [2]. The most commonly used treatment paradigm for NSCLC is chemotherapy, or chemotherapy with the help of targeted treatments such as anti-PD-L1 antibodies when patients are detected PD-L1 expression positive [3]. As an immune checkpoint, programmed cell death protein 1 (PD-1) is a glycoprotein which expresses on lymphocytes to inhibit immune responses and activate apoptosis of antigen-specific T cells. Programmed death ligand 1 (PD-L1) is the glycoprotein which expresses on many tumor cells and compromises the proliferation of PD-1 positive cells [4]. By binding PD-L1 with PD-1 on lymphocytes, it allows tumor cells to evade immune detection and further causes damage to human body [5]. Whether the PD-L1 expression in NSCLC patients is positive or negative, plays an essential role in clinical treatment, considering the fact that anti-PD-L1 antibodies treatment is currently a more efficient reach to those who are positive in PD-L1 expression [6].

For the sake of treating more advanced NSCLC cases, patient categorization needs to be made based on PD-1/PD-L1 expression. Using targeted anti-PD-L1 antibodies on patients who are not detected PD-L1 expression positive would only cause treatment related toxicity and economic cost. Currently, there are four most common ways to assort patients into different cohort.

Tissue biopsy is used to determine cancerous cells, in addition, showing the percentage of PD-L1 expression. However, only using biopsy when determining cancer cells

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could create selection bias – since the PD-L1 expression could differ between primary tumor and metastatic tumors; one sample of tumor in a patient showing positive in PD-L1 expression does not mean that all the other metastasis tumor cells are all have the same expression > 1%. The within patients and inter-tumor heterogeneity would lower the clinical efficacy of anti-PD-L1 antibody treatments on patients who has PD-L1 expression > 1% (TPS) [7].

Not the same as biopsy which can only examine one piece of tumor cells, Positron emission tomography/computed tomography (PET/CT) and single-photon emission computerized tomography/computed tomography (SPECT/CT) are advanced imaging tests which help reveal the metabolic or biochemical function using radioactive drugs, detecting abnormal metabolic activities in human bodies such as unusual uptake value (SUVmax) from tumor cells [8]. They allow tumor cells all over the body to be examined with the help of 18FDG, determining the malignance of tumor cells. However, the PD-L1 expression cannot be examined using 18FDG as the radiomic tracer due to the fact that the tracer does not bind to any PD-L1 glycoproteins [9]. Therefore, using anti-PD-L1 antibodies as the radio tracer appeared as a pilot reach to go with the PET/CT and SPECT/CT. It is a prospective approach because antibody radio tracer allows itself to bind with PD-L1 and showing the SUVmax correlated with the PD-L1 expression [10].

As the most recently breakthrough, radiomic analysis can also be used to select patients pre and during treatments. However, this technology is still requiring improvements – it is easy to determine high or low expression of PD-L1 but lacking the ability to determine positive or negative PD-L1 expression (between expressions ≥ 1%-49% and <1%) [11].

According to my knowledge, it is the first meta-analysis to investigate the correlation between the PD-L1 antibody radiotracer in use of PET/CT & SPECT/CT and PD-1/PD-L1 expression to evaluate the treatment efficacy of the PD-1/PD-L1 antibody in NSCLC patients.

2. Material and Methods

2.1. Literature Search

Two independent researchers have searched Cochrane Library, PubMed, Google Scholar, and Embase databases from 01 January 2012 to 01 July 2022, and obtained clinical trials that included the usage of different radio tracers to determine PD-L1 expressions with PET/CT and SPECT/CT, and those which used single or any combination of anti-PD-L1 therapies to the patients. The included keywords are PD-L1, PD-1, NSCLC, biopsies, radio tracers, Pembrolizumab, KEYTRUDA, Atezolizumab, Nivolumab, PET/CT, and SPECT/CT.

2.2. Study Selection

Throughout this meta-analysis, the following inclusion criteria are defined: 1. Clinical trials that are in-patients with NSCLC; 2. Research papers that reported data of patients' demographic for further HR, OS and PFS models, clinical efficacy, and any grades of adverse events (AEs). 3. Peer-reviewed journals that randomized controlled trials; The intervention arms that included any single or combination treatments of anti-PD-L1/ PD-1 antibody or labeled radio tracers; 4. Papers with outcomes included the correlation between the antibody-labeled radiotracer intake and FPS/OS prognosis, and the correlation between antibody labeled radio tracer intake and PD-1/PD-L1 expression. The following exclusion criteria are defined:

1) Papers that are published in other languages except English;
2) Papers that do not support their results with original data;
3) Research that performed their experiment only on animals, or the full text could not be found. This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline.

2.3. Data Extraction

The data are extracted by two independent authors: year of publication, name of the first author, trial phases from I to II, histology of lung cancer, patient demographic included with age, HR, PFS, OS, clinical efficacy, ECOG PS, and any grades of adverse events (AEs), drugs that were studies, total number of patients that were evaluated for safety, the dosage of radiotracers and scanning protocols of certain SPECT/CT and PET/CT. The third author will access the data and resolve the disagreement when arguments arise.

2.4. Assessment of Study Quality

The study quality of the research papers that the two independent authors gathered have passed The Cochrane Collaboration's RCT bias risk tool, and each has been proven as low risk of bias by two independent authors. The GRADE approach was selected to examine the overall quality of the data.

2.5. Statistical Analysis

All the statistical analysis were done by SPSS, and 0.05 was the cut-off value used to evaluate. We adopted Hazard Ratios (HR) to determine the risks of OS and PFS and used Odds Rations (ORs) to evaluate the risks of AEs and 95% confidence intervals (CIs) were calculated for each item. Statistical heterogeneity among different research was determined by Cochrane Q and I^2 statistics. Heterogeneity was considered low or high for $I^2 < 50\%$ and $I^2 > 50\%$; if $I^2 > 50\%$, the random effect model was selected. When there is a significant heterogeneity in the study, a random model is used, reported using DerSimonian and Laird method. Subgroup analysis was performed to evaluated histology, and treatment regimen. The significance of subgroup analysis was determined by the Mantel-Haenszel method.

3. Results

Two independent authors have determined the eligibility of the articles for more reviews. In conclusion, a summary of 260 articles were examined using primary search strategies, and all the articles could be found on PubMed, Google Scholar, Cochrane Library, and Embase databases. There are 92 articles left after removing duplicates that are not relevant to this study – 62 review papers are removed; 36 meta-analysis are excluded; 37 trial reports are isolated, and 33 editorials are omitted. Eventually, this study has concluded 4 published clinical trials that included a sum of 50 patients and 6 human NSCLC samples (Figure 1).

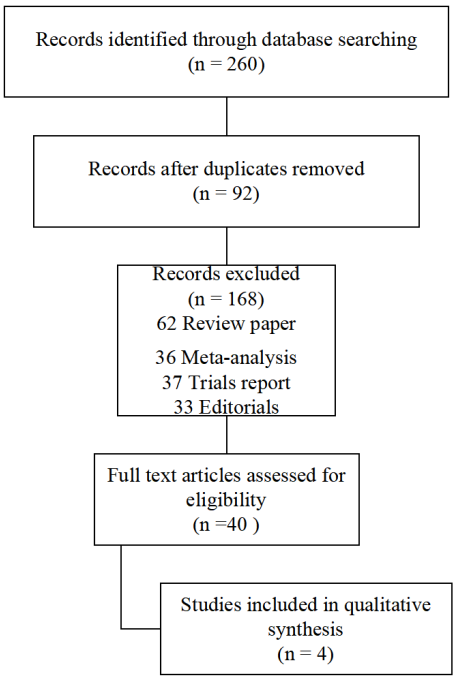

Figure 1. Flowchart of Study Selection: From Database Identification to Final Inclusion.

The characteristics of all 4 included research are listed in Table 1. From all the articles, one is published in 2019, one in 2017, one in 2021, and one in 2018. Examined by two authors independently, all clinical trials are open labeled, randomized, and during phase I. The first and fourth papers involved anti-PD-L1 antibodies (^{99m}Tc-Labeled and atezolizumab), while the second clinical trial included ^{18}F-labeled Adnectin as the treatment arm, and the third paper included an-PD-1 antibody (pembrolizumab) as the study arm. Also, trial that used ^{99m}Tc-Labeled Anti-PD-L1 as treatment injected 3.8-8.4 MBq/kg with an addition of 200 μg NM-01 for cohort 1, and later adjusted the dosage (99mTc-NM-01 9.1-10.4 MBq/kg, 5.6–6.1 μg/kg; NM-01 400 μg) for cohort 2. Research 3 has used 37MBq of ^{89}Zr-pembrolizumab for the first cohort and later added an addition of 2 mg pembrolizumab for the second cohort.

Table 1. Summary of Included Studies in the Qualitative Synthesis.

Names of Treatments	Author and Year	Registered No.	Phase of Trials	Study Arms	No. of Patients	Histology
^{99m}Tc-Labeled Anti-PD-L1	Yan Xing, 2019	NCT02978196	I	99mTc-NM-01 3.8-8.4 MBq/kg, 1.2–2.1 μg/kg; NM-01 200 μg 99mTc-NM-01 9.1-10.4 MBq/kg, 5.6–6.1 μg/kg; NM-01 400 μg	16	NSCLC
^{18}F-labeled Adnectin	David J. Donnelly, 2017		I	18F-Labeled Adnectin (18F-BMS-986192); ADX_5322_A02 anti-PD-L1	6 Human NSCLC samples	NSCLC

^{89}Zr-pembrolizumab	Anna-Larissa Niemeijer, 2021	NCT03065764	I	Adnectin 3 mg/kg 89Zr-pembrolizumab 37MBq ± 10% 89Zr-pembrolizumab 37MBq ± 10%; pembrolizumab 2 mg	12	NSCLC
^{89}Zr-atezolizumab	Frederike Bensch, 2018	NCT02453984 and NCT02478099	I	Unlabeled atezolizumab 10 mg; 89Zr-atezolizumab 37 MBq	22	NSCLC

In NSCLC patients with T:BP ratio as the cut off value, the mean value of T:BP ratio was 2.005 (range 1.24-3.53, P = 0.005). The T:BP ratio within patients who are diagnosed with PD-L1 expression positive is greater than PD-L1 expression negative patients (2.49 vs 1.89, P = 0.048). In NSCLC patients with SUVmax as the cut off value measurement, the mean value of SUVmax in research 3 is 11.5 (range 10.1-12.9) at 1h, and 3.3 (range 1.868-4.732) through day 3 to 7. In research 4, the mean value of SUVmax is 10.4 (range 1.6-46.1).

The association between the PD-L1 expression and prognosis can not be validated directly due to the heterogeneity of PD-L1 expression of the primary and metastatic tumor site; and the PD-L1 positive value (>1% TPS score） can not evidently predict the overall efficacy and prognosis of the PD1/PD-L1 treatment.

The association between the T:BP ratio, SUVmax and prognosis can be validated based on the above-mentioned statistics; according to the pooled data; the T:BP ratio above 2.5 at 2 hour and SUVmax above 3.5 can indicate the poorer prognosis compared with the control group based on the ECOG criteria (OR: 2.37 and 3.35 respectively).

4. Discussion

Using anti-PD-1/PD-L1 antibody labeled radio tracer as the radioligand is an innovative approach to patients who have NSCLC. In many clinical trials in records, the result of PET scan using such radio tracer could be more comprehensive than the result of normal tumor biopsy due to its heterogeneity [12]. In addition, the stability and credibility of such method still needs further testing and analysis.

The prognosis of patients has positive correlations with the SUVmax or T:BP ratio. According to data analysis above, the results of SUVmax or T:BP ratio has a better ability to evaluate a patient's PD-1/PD-L1 expression compared to tumor tissue biopsy, because of the heterogeneity that tumor biopsy can create. Patients who are diagnosed with PD-L1 positive (>1%, <50%) using biopsy sometimes show an insufficient progression on tumor cell [13,14], due to the possibility that different metastases tumor cells have diverse PD-L1 expression, and tumor biopsy creates selection bias.

Furthermore, comparing to tissue biopsy, PET/CT and SPECT/CT have its own advantages: PET scan is a generally comprehensive approach to determine TPS, which can precisely examine the number of metastases tumors and their locations; also, each metastases tumor cells' PD-L1 expression can be well inspected [15]. Comparing to tissue biopsy that are invasive, PET/SPECT CT scans are non-invasive and painless to patients which only requires the intravenous injection of radioligand. Additionally, the usage of different type of radioligand is contemporary. Compare to 18FDG which cannot directly shows the expression of PD-L1 by looking at the SUVmax or T:BP ratio, anti-PD-L1 antibody labeled radio tracer is highly specified and sensitive, that is capable of showing its expression of PD-L1.

However, there are still limitations to this approach. First, the cut off values of such methods are not unified. There are clinical trials that use SUVmax as standards [16], and others use T:BP ratio [13]. Even though the standards are the same, the cut off values are still dissimilar in different research, which created hardships in promoting this method to the world. Second, the long term effect of this radioligand is still uncertain and lack of information and research. Thirdly, there are also lack of information of non-naïve patients. Most of the clinical research recorded are using mostly naïve patients, who have not yet received any treatments before, which limited this current method to naïve patients only.

This meta-analysis has its own strengths and drawbacks. According to existing meta-analyses, this is the first meta-analysis that write about anti-PD-L1 antibody labeled radio tracer's effects on diagnosing NSCLC patients. In addition all research that are included as databases of this article are all clinical trials, and most of them are in-human research, which make this analysis more credible. Also, a lot of statistical models are used to make this paper as accurate as possible. However, there are still drawbacks of this paper: Due to the novel of the topic, most of the research that are used as databases are processing under sampling, and research heterogeneity exist due to the difference between patients (age, gender, and other characteristics) and variables used in each research.

Except PET/SPECT CT scan, there are future expectations in this field to identify different patients in an accurate way. Radiomics – texture analysis could be a leading course [17]. By using radiomics, it can accurately predict the treatment efficacy of certain patient and their possibility to become cachexia [18]. However, current radiomics has not yet developed a universal parameter, which makes it difficult to use widely. Liquid biopsy is another method that is expected to delve into in the future. The part of patients that need to be identified is the part which has their TPS < 50%, but>1%. Liquid biopsy is very sensitive to those who has high positive PD-L1 expression (>50%). However, only using liquid biopsy would be hard to determine whether the patients have TPS > 1% and <50%. Therefore, a combination of liquid biopsy and antibody labeled radio tracer PET scan could provide an accurate and comprehensive result of the patients.

5. Conclusion

In conclusion, this meta-analysis concluded the innovative method to identify patients with TPS < 50% and >1%, and the strength of it comparing to the casual tumor tissue biopsy. In spite of the limitations and drawbacks this paper has, it suggests that anti-PD-1/PD-L1 antibody labeled radio tracer has a better usage on classifying patients with NSCLC compared to normal radioligand, and PET scan can provide a comprehensive result compared to normal biopsy.

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